

R E M A R K S

Claims 1, 4, 5 and 8 to 21 as set forth in Appendix II of this paper are now pending in this case. Claims 2, 3 and 7 have been canceled, Claims 1, 4, 5 and 8 to 12 have been amended, and new Claims 13 to 21 have been added as indicated in in the Listing of Claims set forth in Appendix I of this paper.

Accordingly, applicants have amended Claim 1 to recite the features previously provided by Claims 2, 3 and 7. Additionally, the expression "*regular dialysis*" has been replaced by --intermittent dialysis-- as supported by applicants' disclosure on page 12, indicated lines 37 and 38, of the application. The wording of Claim 4 has been revised to better bring out that the half-life of PEG-hirudin has at least a value of about 4 hours, and the expression "*is prolonged at least about*" in Claim 11 has been replaced by --is at least prolonged about--. New Claims 13 to 21 have been added to further bring out some of the embodiments of applicants' method which are addressed on page 20, indicated line 21, to page 26, indicated line 9, of the application. No new matter has been added.

The Examiner has rejected Claims 4, 5 and 11 under Section 112, 2, contending that the expression "*at least about 4 hours*" renders the claimed subject matter indefinite. Favorable reconsideration of the Examiner's position and withdrawal of the respective rejection is respectfully solicited in light of applicants' amendment which changes the wording to "*at least a value of about 4 hours*" which clearly brings out the minimum requirements which the half-live has to meet in accordance with the provisions of Claim 4, and the corresponding revision of the wording in Claim 11 to better bring out the minimum requirement for the APTT prolongation. Favorable action is solicited.

The Examiner has rejected Claims 1 to 5 and 12 under Section 102(b) as being anticipated by the teaching of *Kurfürst et al.* (US 5,663,141). Favorable reconsideration of the Examiner's position and withdrawal of the rejection is respectfully solicited in light of applicants' amendment and the following remarks.

The teaching of *Kurfürst et al.* relates to PEG-hirudin and its applications. With regard to the use of PEG-hirudin in hemodialysis, *Kurfürst et al.* refer to the application in extracorporeal circulation¹⁾ which aims at preventing the formation of thrombi when the blood is circulated extracorporeally.

Applicants' method is particularly adapted for the treatment of subjects which require recurring hemodialysis due to a chronic renal insufficiency, and is distinguished from the disclosure provided by *Kurfürst et al.* in the requirement that PEG-hirudin is applied in an amount which is effective to prevent the formation of thrombi during the extracorporeal phase of an intermittent hemodialysis therapy, and which is also effective for the prophylaxis of vascular complications during the period between hemodialysis treatments.

The test for anticipation is one of identity, and the identical invention must be shown in the art in as complete detail as is contained in the claim²⁾. In fact, the Federal Circuit has stated that it is error to treat claims as a catalog of separate parts, in disregard of the part-to-part relationships set forth in the claims that give those claims their meaning³⁾. The teaching of *Kurfürst et al.* clearly fails to identically show applicants' method in as complete detail as defined in Claim 1 as herewith presented. The disclosure of *Kurfürst et al.* therefore cannot be considered to amount to an anticipatory disclosure within the meaning of Section 102 where the subject matter of Claim 1 is concerned. Claims 4, 5 and 8 to 12 incorporate the requirements of Claims 1 by reference, and new Claims 13 to 21 recite similar requirements. The teaching of *Kurfürst et al.*, therefore, equally fails to anticipate the subject matter of Claims 4, 5 and 8 to 21. Favorable action is solicited.

The Examiner has rejected Claims 1 to 5 and 7 to 12 under 35 U.S.C. §103(a) as being unpatentable in light of the disclosure of *Kurfürst et al.* (US 5,663,141) when taken in view of the teachings of *Maraganore et al.* (US 5,256,559), *DeRosa et al.* (US 5,723,576) and *Fischer et al.* (Kidney Int., 56(72), 46-50 (1999)).

1) For example, col. 5, indicated lines 37 to 44, of US 5,663,141.

2) I.e. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 9 USPQ2d 1913 (CAFC 1989).

3) I.e. *Lindemann Maschinenfabrik v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (CAFC 1984).

As mentioned in the foregoing, *Kurfürst et al.* are not concerned with the intricacies involved in the therapy of subjects suffering from chronic renal insufficiency which requires recurring hemodialysis treatments. The teaching of *Kurfürst et al.* therefore cannot be considered to suggest or imply applicants' method wherein the PEG-hirudin is applied to the subject in amounts which not only protect against the formation of thrombi during the hemodialysis phase when the blood is circulated extracorporeally, but which also protect the subject in the period between hemodialysis treatments against vascular complications.

The same applies, *mutatis mutandis*, to the teaching of *Maragamore et al.* *Maragamore et al.* mention that pegylated hirudins are useful alone, or in compositions or combinations, for the treatment and prophylaxis of vascular diseases attributed to thromboses⁴⁾, and that pegylated hirudins, or compositions containing them, may be used to inhibit platelet aggregation in extracorporeal blood⁵⁾. *Maragamore et al.* is, however, not concerned with intermittent hemodialysis which is necessary to treat a subject suffering from chronic renal insufficiency. The teaching of *Maragamore et al.* therefore does not close, or even narrow, the gap between the teaching of *Kurfürst et al.* and applicants' method.

The disclosure of *DeRosa et al.* relates to hirudin analogs named "hirunorms" and does not address PEG-hirudin. Additionally, like the teaching of *Maragamore et al.* and the teaching of *Kurfürst et al.*, the teaching of *DeRosa et al.* is equally not concerned with the intricacies involved in the treatment with intermittent hemodialysis of a subject suffering from chronic renal insufficiency. It merely provides that the "hirunorms" can be used to prevent venous and arterial thrombosis and to disseminate intravascular coagulation, and that the "hirunorms" can be used in extracorporeal circulation. As such, the disclosure of *DeRosa et al.* therefore does not add anything to the teaching of *Kurfürst et al.* and the teaching of *Maragamore et al.* where a method of treating a subject suffering from chronic renal insufficiency is concerned.

The same applies, *mutatis mutandis*, where the teaching of *Fischer et al.* is concerned. *Fischer et al.* address the anticoagulant

4) For example, col. 9, indicated lines 20 to 24, of *US 5,256,229*.

5) For example, col. 9, indicated lines 34 to 36, of *US 5,256,559*.

effects of recombinant hirudin when applied in continuous hemodialysis. Continuous hemodialysis is used in the treatment of subjects suffering from acute renal failure. In such cases, hemodialysis is applied once for a prolonged period of time. In contrast to the treatment of acute renal failure, chronic renal insufficiency requires repeated hemodialysis treatments ("intermittent hemodialysis"), and the dialysis treatments have to be repeated in most cases of chronic renal insufficiency throughout the life of the subject. It is the repetition of the hemodialysis and the extracorporeal circulation of blood required therefore, which causes over time an accumulation of vascular events and ultimately results in life-threatening vascular complications⁶).

Fischer et al.'s disclosure therefore also fails to provide information which is pertinent to an intermittent hemodialysis treatment.

None of the references applied by the Examiner in the rejection under Section 103(a) deal with the particular circumstances which characterize the treatment of chronic renal insufficiency and which are pertinent to a treatment by intermittent hemodialysis. The teaching of *Kurfürst et al.*, when taken in view of the disclosure of *Maraganore et al.*, *DeRosa et al.* and *Fischer et al.* therefore does not provide a person of ordinary skill in the art with the information which is necessary to arrive at applicants' method. Favorable reconsideration of the Examiner's position and withdrawal of the rejection under Section 103(a) is respectfully solicited.

REQUEST FOR EXTENSION OF TIME:

It is respectfully requested that a one month extension of time be granted in this case. A check for the \$110.00 fee is attached.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit

6) Note, for example, applicants' explanations on page 3, indicated line 12, to page 4, indicated line 1, of the replacement specification submitted on February 25, 2003. As stated there, the mortality due to vascular complications of subjects treated with intermittent hemodialysis is 12%, and the average life expectancy of such subjects is 6 years.

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SCHERHAG et al.

0480/01227

Account No. 11.0345. Please credit any excess fees to such deposit account.

Respectfully submitted,

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Encl.: THE LISTING OF CLAIMS (Appendix I)
THE AMENDED CLAIMS (Appendix II)

HBK/BAS

A P P E N D I X I:

THE LISTING OF CLAIMS (version with markings, showing the changes made):

1. (currently amended) A method for the [~~prophylactic-anticoagulant~~] treatment of a subject [~~whose blood has undergone~~] suffering from chronic renal insufficiency, the subject requiring intermittent hemodialysis comprising extracorporeal circulation of blood, wherein an [~~anticoagulant~~] effective amount of PEG(polyethylene glycol)-hirudin is administered to said subject for effective anticoagulant protection during the extracorporeal circulation and for prophylaxis of vascular complications after the extracorporeal circulation.
2. (canceled)
3. (canceled)
4. (currently amended) [A] The method [~~as-claimed-in~~] of claim 1, wherein the [~~anticoagulant-agent~~] PEG-hirudin has a terminal half-life [~~of~~] having at least a value of about 4 hours.
5. (currently amended) [A] The method [~~as-claimed-in~~] of claim 4, wherein the [~~anticoagulant-agent~~] PEG-hirudin has an enduring anticoagulant pharmacodynamic activity.
6. (canceled)
7. (canceled)
8. (currently amended) [A] The method [~~as-claimed-in~~] of claim [7] 1, wherein the PEG-hirudin is administered in [~~the~~] form of a single dose per hemodialysis.
9. (currently amended) [A] The method [~~as-claimed-in~~] of claim 8, wherein the single dose is administered at the start of the hemodialysis.
10. (currently amended) [A] The method [~~as-claimed-in~~] of claim 8, wherein the amount of the single dose administered for a hemodialysis is such that the activated thromboplastic time (APTT) is prolonged about 2.7-fold to about 1.8-fold during the hemodialysis.
11. (currently amended) [A] The method [~~as-claimed-in~~] of claim 8, wherein the amount of the single dose administered for a hemodialysis is such that the APTT is at least prolonged [~~at least~~] about 1.2-fold until the next hemodialysis.

12. (currently amended) The method of claim 1, wherein [~~in which~~] the PEG-hirudin is derived from recombinant hirudin.
13. (new) A method of treating an individual suffering from chronic renal insufficiency, which comprises subjecting said individual to intermittent hemodialysis comprising repeating cycles of
an extracorporeal phase wherein blood of said individual is circulated extracorporeally, and
an intracorporeal phase wherein no blood of said individual is circulated extracorporeally,
and administering to said individual an effective amount of PEG(polyethylene glycol)-hirudin, said effective amount being adapted to provide for an effective anticoagulant protection during the extracorporeal phase, and for an effective prophylaxis of vascular complications during the intracorporeal phase.
14. (new) The method of claim 13, wherein the PEG-hirudin is administered such that, at the end of the intracorporeal phase, a PEG-hirudin blood level having at least a value of about 150 ng/ml is obtained.
15. (new) The method of claim 13, wherein the PEG-hirudin is administered such that, at the end of the intracorporeal phase, a PEG-hirudin blood level having at least a value of about 300 ng/ml is obtained.
16. (new) The method of claim 13, wherein the effective amount is administered in form of a single dose per cycle.
17. (new) The method of claim 16, wherein the single dose is administered at the start of the extracorporeal phase.
18. (new) The method of claim 16, wherein the effective amount is adapted such that, during the intracorporeal phase, a PEG-hirudin blood level of about 150 ng/ml to 2000 ng/ml is obtained.
19. (new) The method of claim 16, wherein the effective amount is adapted such that the activated thromboplastic time (APTT) is prolonged about 2.7-fold to about 1.8-fold during the extracorporeal phase.
20. (new) The method of claim 16, wherein the effective amount is adapted such that the APTT is at least prolonged about 1.2-fold during a hemodialysis cycle.

21. (new) The method of claim 13, wherein the PEG-hirudin is derived from recombinant hirudin.

A P P E N D I X II:

THE AMENDED CLAIMS (clean version of all claims):

1. (currently amended) A method for the treatment of a subject suffering from chronic renal insufficiency, the subject requiring intermittent hemodialysis comprising extracorporeal circulation of blood, wherein an effective amount of PEG(polyethylene glycol)-hirudin is administered to said subject for effective anticoagulant protection during the extracorporeal circulation and for prophylaxis of vascular complications after the extracorporeal circulation.
2. (canceled)
3. (canceled)
4. (currently amended) The method of claim 1, wherein the PEG-hirudin has a terminal half-life having at least a value of about 4 hours.
5. (currently amended) The method of claim 4, wherein the PEG-hirudin has an enduring anticoagulant pharmacodynamic activity.
6. (canceled)
7. (canceled)
8. (currently amended) The method of claim 1, wherein the PEG-hirudin is administered in form of a single dose per hemodialysis.
9. (currently amended) The method of claim 8, wherein the single dose is administered at the start of the hemodialysis.
10. (currently amended) The method of claim 8, wherein the amount of the single dose administered for a hemodialysis is such that the activated thromboplastic time (APTT) is prolonged about 2.7-fold to about 1.8-fold during the hemodialysis.
11. (currently amended) The method of claim 8, wherein the amount of the single dose administered for a hemodialysis is such that the APTT is at least prolonged about 1.2-fold until the next hemodialysis.
12. (currently amended) The method of claim 1, wherein the PEG-hirudin is derived from recombinant hirudin.

13. (new) A method of treating an individual suffering from chronic renal insufficiency, which comprises subjecting said individual to intermittent hemodialysis comprising repeating cycles of an extracorporeal phase wherein blood of said individual is circulated extracorporeally, and an intracorporeal phase wherein no blood of said individual is circulated extracorporeally, and administering to said individual an effective amount of PEG(polyethylene glycol)-hirudin, said effective amount being adapted to provide for an effective anticoagulant protection during the extracorporeal phase, and for an effective prophylaxis of vascular complications during the intracorporeal phase.
14. (new) The method of claim 13, wherein the PEG-hirudin is administered such that, at the end of the intracorporeal phase, a PEG-hirudin blood level having at least a value of about 150 ng/ml is obtained.
15. (new) The method of claim 13, wherein the PEG-hirudin is administered such that, at the end of the intracorporeal phase, a PEG-hirudin blood level having at least a value of about 300 ng/ml is obtained.
16. (new) The method of claim 13, wherein the effective amount is administered in form of a single dose per cycle.
17. (new) The method of claim 16, wherein the single dose is administered at the start of the extracorporeal phase.
18. (new) The method of claim 16, wherein the effective amount is adapted such that, during the intracorporeal phase, a PEG-hirudin blood level of about 150 ng/ml to 2000 ng/ml is obtained.
19. (new) The method of claim 16, wherein the effective amount is adapted such that the activated thromboplastic time (APTT) is prolonged about 2.7-fold to about 1.8-fold during the extracorporeal phase.
20. (new) The method of claim 16, wherein the effective amount is adapted such that the APTT is at least prolonged about 1.2-fold during a hemodialysis cycle.
21. (new) The method of claim 13, wherein the PEG-hirudin is derived from recombinant hirudin.